REMARKS

Claims 136-159, 162-170, 173-190, 193-197 and 202-204 were pending and claims 160, 161, 171, 172, 191, 192 and 198-201 were withdrawn from consideration. In the instant amendment, non-elected claims 160, 161, 171, 172, 191, 192 and 198-201 have been canceled, without prejudice (as discussed in Section II below). Claims 136, 173 and 193 have been amended. Upon entry of the amendment, claims 136-159, 162-170, 173-190, 193-197 and 202-204 will be pending and under consideration.

I. AMENDMENT TO THE SPECIFICATION

The title of the specification has been amended to conform with the subject matter to which the elected claims are directed. As the amended title does not introduce new matter, entry thereof is respectfully requested.

The first paragraph following the title has been amended to recite that "[t]his application claims the benefit of U.S. Provisional application Serial No. 60/296,499, filed June 6, 2001, the disclosure of which is incorporated herein by reference." Support for this amendment is found in the application and accompanying transmittal papers as filed. Applicants kindly request entry of the amendment to the claim of priority in the first paragraph following the title of the instant specification. Applicants will present a new oath or declaration reflecting the changes in priority prior to allowance.

The abstract of the disclosure has been amended to include the general structure of the compound encompassed in claim 136 and the general nature of its use, including reference to methods using the compound for treatment of inflammatory and immunoregulatory disorders and diseases. The abstract is fully supported by the specification as filed and does not introduce new matter. Entry of the amended abstract is respectfully requested.

II. AMENDMENT TO THE CLAIMS

Claims 160, 161, 171, 172, 191, 192 and 198-201 have been canceled to conform to elected subject matter in Applicant's Response to Restriction Requirement, mailed March 11, 2003, and the claim cancellation is made without prejudice to Applicant's right to pursue non-elected subject matter in one or more related applications including divisional, continuation, or continuation-in-part applications.

In relevant part, amended claim 136 recites that "X is -C(O)- or -CH_2-." Claim 136 has been amended to conform to elected subject matter in Applicant's Response to Restriction Requirement, mailed March 11, 2003, and is made without prejudice to

Applicant's right to pursue non-elected subject matter in one or more future filed divisional, continuation, or continuation-in-part applications.

Claim 136 and claim 173 have been amended to recite, in relevant part, "a compound . . . or a pharmaceutically acceptable salt thereof wherein: . . . ."

Claim 193 has been amended to depend from claim 188.

As the above amendments to claims are fully supported by the specification and claims as originally filed, entry thereof is respectfully requested. No new matter has been added. No amendment fee is believed to be due.

III. RESPONSE TO OBJECTIONS ARISING UPON ELECTION/RESTRICTION

A. Withdrawn Claims

Applicants respectfully submit that a typographical error is present on page 3 of the Office Action mailed May 30, 2003, where the Patent Office includes claim 202 in the set of withdrawn claims. Since claim 202 was included among the elected subject matter in Applicant's Response to Restriction Requirement, mailed March 11, 2003, Applicants kindly request that the record reflect that claim 202 is not withdrawn.

B. Objections To Claims Containing Non-Elected Subject Matter

The Patent Office objects to claims 136, 138, 140-159, 162-170, 187-190, 193-197, and 202-204 as containing non-elected subject matter to the extent that claim 136 recites X = a bond. Applicants respectfully submit that the instant amendment to claim 136 removes non-elected subject matter. This amendment to claim 136 obviates the objection to claims 138, 140-159, 162-170, 187-190, 193-197, and 202-204 that depend from claim 136. Accordingly, Applicants respectfully request that the objection to claims 136, 138, 140-159, 162-170, 187-190, 193-197, and 202-204 be withdrawn.

IV. RESPONSE TO OBJECTIONS REGARDING THE SPECIFICATION

A. Title

The Patent Office states that the title of the invention is not descriptive and that a new title is required that is clearly indicative of the invention to which the claims are directed after restriction. Applicants have amended the title of the specification to conform with the invention to which the claims are directed. Accordingly, Applicants respectfully request withdrawal of the objection.

B. Abstract

The Patent Office requests a revised abstract of the disclosure in the instant application. A revised abstract has been submitted for entry, as detailed above. Applicants submit that the revised abstract contains the proper content of an abstract of the disclosure, and therefore Applicants respectfully request that the objection to the abstract of the disclosure be withdrawn.

C. Priority Under 35 U.S.C. § 119(e)

The Patent Office alleges that Provisional Application 60/255,241 and Provisional Application 60/296,499 fail to provide adequate support under 35 U.S.C. § 112 for a claim of priority under 35 U.S.C. § 119(e) with respect to the pending claims. As reflected by the instant amendment to the first paragraph of the specification described above, Applicant withdraws any claim of priority under 35 U.S.C. § 119(e) to Provisional Application 60/255,241 with respect to claims 136-159, 162-170, 173-190, 193-197 and 202-204. Accordingly, Applicant respectfully requests that the objection with regard to a claim of priority to Provisional Application 60/255,241 be withdrawn.

Applicant traverses the objection with regard to Provisional Application 60/296,499, and submits that Provisional Application 60/296,499 provides adequate support under 35 U.S.C. § 112 for a claim of priority under 35 U.S.C. § 119(e) with respect to claims 136-159, 162-170, 173-190, 193-197 and 202-204.

The Patent Office alleges that the figures on page 14 of Provisional Application 60/296,499 do not support the formula recited in the instant claim 136 where constituent X is a $-CH_2-$ group. Further, the Patent Office alleges that claim 62 of the Provisional Application 60/296,499 "teaches away" from constituent X being a $-CH_2-$ group. "Teaching away" is a relevant consideration for an analysis pursuant to 35 U.S.C. § 103, but not for analysis under 35 U.S.C. § 112. Section 119 of Title 35 of the Code, like § 120, explicitly requires only that the claimed subject matter be "disclosed in the manner provided by the first paragraph of section 112," thus Applicants may claim priority if Provisional Application 60/296,499 discloses what is presently claimed. *See, e.g., In re Brower*, 167 U.S.P.Q. 684 (C.C.P.A. 1970); *Ex parte Maziere*, 27 U.S.P.Q.2d 1705 (Bd. Pat. App. 1993); MPEP § 2172 (III). In fact, Provisional Application 60/296,499 provides adequate written support for what is presently claimed.

As acknowledged by the Patent Office, claim 51 of Provisional Application 60/296,499 discloses the formula recited in the instant claim 136 where

constituent X is a $-CH_2-$ group. The structure recited in claim 136 is encompassed in formula (I) on page 12, the A-ring scaffold on page 13, and is identical to formula (III) on page 17 of the Provisional Application 60/296,499, where the constituents of the structure recited in claim 136 are fully disclosed in the accompanying discussion on pages 12-19 of the Provisional Application 60/296,499. Thus, claims 136-159, 162-170, 173-190, 193-197 and 202-204 are fully supported by Provisional Application 60/296,499 in conformity with the requirements of 35 U.S.C. § 112. Specific support in Provisional Application 60/296,499 for the X, A^4, R^3 and R^{14} constituents of the formula recited in claim 136 are cited below.

Constituent X of the structure of claim 136 can be C(O) or CH_2, which are two of the three embodiments for X as stated on page 18, lines 10-12 of Provisional Application 60/296,499. The reason that claim 136 does not recite all three embodiments is a result of the instant Amendment to conform to the elected subject matter of the Restriction Requirement imposed by the Patent Office.

A^4 in formula (III) on page 17, line 26, of the Provisional Application 60/296,499 can be C or N. In claim 136 of the instant Application, the N embodiment is recited for A^4.

Claim 136 recites that R^3 is a member selected from the group consisting of hydroxy, (C_1-C_8)alkoxy, amino, (C_1-C_8)alkylamino, di(C_1-C_8)alkylamino, (C_2-C_8)heteroalkyl, (C_3-C_9)heterocyclyl, (C_1-C_8)acylamino, amidino, guanidino, ureido, cyano, heteroaryl, $-CONR^9R^{10}$ and $-CO_2R^{11}$. The Markush group for R^3 in formula (III) of the Provisional Application 60/296,499 is identical to that recited for R^3 in claim 136. *See, e.g.,* page 12, lines 17-20 and page 18, lines 8-9.

As recited in claim 136, R^{14} is substituted or unsubstituted aryl or heteroaryl. This is supported in the Provisional Application 60/296,499, for example, on page 15, lines 4-5, and page 15, line 34 to page 16, line 1.

The instant amendment to the specification has been amended to state a claim of priority under 35 U.S.C. § 119(e) to Provisional Application 60/296,499, which fully supports instant claims 136-159, 162-170, 173-190, 193-197 and 202-204 under 35 U.S.C. § 112. Accordingly, Applicants kindly request the withdrawal of the objection to Applicant's claim of priority under 35 U.S.C. § 119(e) to Provisional Application 60/296,499.

V. RESPONSE TO CLAIM OBJECTIONS

A. Objection To Claim 189 Under 37 C.F.R. § 1.75

The Patent Office objects to claim 189 under 37 C.F.R. § 1.75 as being duplicative of claim 161. The objection is moot as claim 161 has been canceled without prejudice in the

instant amendment. Therefore, Applicants respectfully request that the objection to claim 189 under 37 C.F.R. § 1.75 be withdrawn.

B. Objection To Claims 156, 157, 170, and 190 Under 37 C.F.R. § 1.75(c)

The Patent Office objects to claims 156, 157, 170 and 190 under 37 C.F.R. § 1.75(c) as being improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully traverse.

The specification states that the present invention is directed to compounds, compositions and methods useful in the modulation of chemokine receptor activity, particularly CXCR3. *See* page 12, lines 25-26. In Figure 19, data are presented for exemplary compounds used in an assay described on pages 162-163 of the specification which demonstrate activity towards CXCR3. However, it is not the function of claims to specifically exclude possible inoperative substances. *See, e.g., Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.,* 224 U.S.P.Q. 409, 414 (Fed. Cir. 1984). Therefore, to the extent that the recited compound of independent claim 136 may be found to encompass a non-CXCR3 modulator, dependent claims 156, 157, 170 and 190 serve to limit the subject matter of claim 136 in accordance with 37 C.F.R. § 1.75. Applicants respectfully request the withdrawal of the objection to claims 156, 157, 170 and 190 under 37 C.F.R. § 1.75(c).

VI. RESPONSE TO CLAIM REJECTIONS

A. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

i. Claims 136-159, 162-170, 173-190, 193-197 and 202-204

Claims 136-159, 162-170, 173-190, 193-197 and 202-204 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for reciting "prodrug." Applicants respectfully disagree and do not acquiesce in this rejection. Nevertheless to expedite prosecution, Applicants have amended the claims and submit that the rejection is obviated in light of the amendment deleting the word "prodrug" from claims 136 and 173 without prejudice. Therefore, Applicants respectfully request the withdrawal of the rejection of claims 136-159, 162-170, 173-190, 193-197 and 202-204 under 35 U.S.C. § 112, second paragraph.

ii. Claims 193 and 194

Claims 193 and 194 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite since claim 187 has insufficient antecedent basis to the phrase "said

organ transplant condition" recited in claim 193. The rejection is obviated in view of the amendment to claim 193 to depend from claim 188 that has sufficient antecedent basis for the phrase in question. Accordingly, Applicants respectfully request that the rejection of claims 193 and 194 under 35 U.S.C. § 112, second paragraph, be withdrawn.

iii. Claims 187, 190 and 202

Claims 187, 190 and 202 stand rejected under 35 U.S.C. § 112, second paragraph, allegedly because the phrase "a CXCR3-mediated condition or disease" recited in claim 187 is indefinite. Applicants respectfully disagree.

The Patent Office contends that extensive clinical research is necessary to identify the patients and diseases that Applicants intend to treat, but this is not the case. CXCR3 has highly selective expression to certain T lymphocytes and to ectopic expression in certain tumors. *See* specification, page 3, lines 1-11. As explained in the specification on page 25, lines 3-20, the mechanisms underlying inappropriate CXCR3 activity may vary, but whether inappropriate CXCR3 activity contributes to, for example, a particular inflammation in one individual, or particular autoimmune dysfunction in another individual, can be determined by measuring the levels of CXCR3-positive cells or of endogenous chemokines that are CXCR3 ligands, such as IP-10 or Mig, in samples from the afflicted individuals. Such assays are well within the abilities of one of skill in the art, and with certain types of disorders or diseases, such as sarcoidosis or multiple sclerosis, the involvement of CXCR3 is already indicted. *See, e.g.*, Agostini *et al.,* 1998 *J. Immunology* 161:6413-6420 (**Exhibit 1**); Sorensen et al., 1999, *J. Clinical Invest.* 103:807-815 (**Exhibit 2**). Thus, extensive clinical research is not needed to identify the patients and diseases encompassed by the claims.

The Patent Office questions the relationship of the specification's listed diseases as being related to CXCR3 and asks, for example, if all infections are CXCR3-related. As stated in specification, a CXCR3-mediated condition or disease is one in which modulation of CXCR3 results in some effect on the underlying condition or disease (*e.g.*, a CXCR3 antagonist results in some improvement in patient well-being in at least some patients). Specification, page 35, lines 18-20. How a particular person's immune system reacts *via* CXCR3 is never assured in any particular circumstance, but this uncertainty is properly attributed to complexities of physiological systems, not indefiniteness of claim language. One of skill in the art resolves the uncertainty in a particular afflicted person's case by performing assays to measure levels of CXCR3-positive cells or endogenous CXC3 ligands, as discussed above. In one situation or individual an infection can be CXCR3-mediated

condition or disease, whereas it may not be in another situation or individual. A CXCR3-mediated condition or disease is implicated, for example, by making an assessment of CXCR3 overactivity as discussed above or, for example, by recognizing the particular symptoms exhibited by the subject as in multiple sclerosis, which is within the abilities of one of skill in the art.

For these reasons, a CXCR3-mediated condition or disease is sufficiently described in the specification and known to those of skill in the art. Accordingly, Applicants respectfully request that the rejection of claims 187, 190 and 202 under 35 U.S.C. § 112, second paragraph, be withdrawn.

B. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

i. Claims 136-159, 162-170, 173-190, 193-197 and 202-204

Claims 136-159, 162-170, 173-190, 193-197 and 202-204 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly because of lack of enablement for "prodrugs" of the claimed compounds. Applicants respectfully disagree and do not acquiesce in this rejection. Nevertheless to expedite prosecution, the claims have been amended. Applicants respectfully submit that the rejection with respect to each claim is obviated in light of the amendment to delete the word "prodrug" from claims 136 and 173 without prejudice. Since the remaining claims do not recite "prodrug," but are rejected for depending upon either claim 136 or claim 173, the rejection is overcome with regard to these claims as well. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 136-159, 162-170, 173-190, 193-197 and 202-204 under 35 U.S.C. § 112, first paragraph.

ii. Claims 154-159, 162-170, 173-190, 193-197 and 202-204

Claims 154-159, 162-170, 173-190, 193-197 and 202-204 stand rejected under 35 U.S.C. § 112, first paragraph, allegedly for requiring undue experimentation to practice across their scope, *i.e.*, non-enablement. In particular, the Patent Office alleges that the specification does not reasonably provide enablement for treating disease using the recited compound. Applicants respectfully traverse.

The Patent Office bears the initial burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). From the outset, Applicants note that the Patent Office's remarks for lack of enablement as requiring undue experimentation, which are discussed below, are directed towards claims 154-159, 162-170, 173-190, 193-197 and 202, each

reciting a method of treating a recited condition or disease. No remarks appear to be directed to claims 203 or 204. Working examples of claims 203 and 204 are described, for example, on pages 162-163 of the specification with exemplary data garnered from such methods shown in Figure 19 of the specification. Since the Patent Office has not specified any basis for the non-enablement of claims 203 or 204, Applicants respectfully request that the rejection of claims 203 and 204 under 35 U.S.C. § 112, first paragraph, be withdrawn.

With respect to the rejection of claims 154-159, 162-170, 173-190, 193-197 and 202 under 35 U.S.C. § 112, first paragraph, Applicants respectfully submit that the disclosure of the specification as filed fully enables one of skill in the art to practice the claims without undue experimentation. For example, the specification describes the compounds from page 13, line 1, to page 20, line 20, and provides a variety of synthesis routes for making the compounds in Figures 1-18 and in the examples from page 33, line 25, to page 162, line 10. Representative diseases to be treated are disclosed at page 25, lines 3-20, and page 25, line 26, to page 26, line 30. Exemplary formulations to be used in treating subjects is found in the specification at page 21, line 16, to page 24, line 26. How one of skill in the art administers the formulated compounds is disclosed by the specification, for example, on page 24, line 30, to page 25, line 25, and page 26, line 31, to page 30 , line 26. A person of skill in the art without undue experimentation would choose the appropriate dose amounts and administration schedule by routine monitoring of the patient taking into account factors such as described on page 27, lines 4-22, for example, the age, body weight, health, etc. Nonetheless, to remove any doubt that no undue experimentation is required to practice claims 154-159, 162-170, 173-190, 193-197 and 202, we address each of the factors from *In re Wands* that, Applicants respectfully submit, when taken together support a finding of no undue experimentation.

a. <u>The Legal Standard</u>

The legal standard for enablement under 35 U.S.C. § 112, first paragraph, requires that the specification teach those in the art to make and use the invention without undue experimentation. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The Federal Circuit elaborated that whether undue experimentation is needed is not a single, simple factual determination, but a conclusion reached by weighing many factual considerations, and listed eight exemplary factors (the "*Wands* factors"). *Id.* The Patent Office applies the *Wands* factors and concludes that undue experimentation is required to practice each of

claims 154-159, 162-170, 173-190, 193-197 and 202. Applicants respectfully submit that an analysis of the *Wands* factors requires the opposite conclusion.

b. Application of the *Wands* Factors To Claims 154-159, 162-170, 173-190, 193-197 and 202

1. *The State of the Prior Art*

The state of the prior art is that there was a clear, pressing medical need for therapeutic agents directed towards CXCR3 as a target in the year 2001 when the instant application was filed. The Patent Office alleges that the state of the art is provided in Carter, 2002 *Curr. Opinion Chem. Biol.* **6**:510-525, who reports that mice lacking CXCR3 receptors developed normally. Upon closer reading, Carter also reports that these same knock-out mice show markedly greater survival time after cardiac allografting. *See* Carter, page 514, left col. The review by Proudfoot *et al.*, 2003, *Sem. Immun.* 15:57-65, briefly summarizes observations from "knock out" mice experiments, and concludes that mice lacking CXCR3 receptors were used to *validate CXCR3 as a target* for allograft rejection. Proudfoot *et al.*, p. 59, left col. & Fig. 2.

Carter also reviews prior reports which explain why CXCR3 is a target for therapeutic agents in other disorders/diseases, including reports connecting CXCR3-mediated activity with chronic obstructive pulmonary disease (COPD), psoriatic arthritis, and experimental autoimmune encephalomyelitis (EAE), an animal model for human multiple sclerosis. Carter, page 514, left col. Indeed, T-cell overactivity *via* CXCR3 and/or its endogenous ligands is a key feature in inflammatory and immune conditions or diseases as recited in, for example, claim 154. *See, e.g.*, specification, page 3, lines 1-11; Carter, page 514, left col. and citations therein; Agostini *et al.,* 1998 *J. Immunology* 161:6413-6420 (**Exhibit 1**); Sorensen et al., 1999, *J. Clinical Invest.* 103:807-815 (**Exhibit 2**); Balashov *et al.*, 1999, *Proc. Natl. Acad. Sci. USA* 96:6873-6878 (**Exhibit 3**); Qin *et al.*, 1998, *J. Clin. Invest.* 101:746-754 (**Exhibit 4**); Shields *et al.*, 1999, *J. Immunology* 163:6236-6243 (**Exhibit 5**); Gerard & Rollins, 2001, *Nature Immunology* 2:108-115 (**Exhibit 6**). Thus, the observations by Onuffer & Horuk, 2002, *Trends Pharmaco. Sci.* 23:459-467 and Proudfoot *et al.* that are cited by the Patent Office to the effect that CXCR3 antagonists were subject to drug development programs but few antagonists were known and that only antagonists to other chemokine receptors were in clinical trials underscores that the medical/scientific community clearly sought CXCR3 antagonists since CXCR3 was a target for the treatment of CXCR3-mediated conditions and diseases. The instant application discloses a solution. Applicants submit that

this *Wands* factor weighs in favor of enablement of the disclosure when viewed in light of other factors which lean in Applicant's favor.

2. ***The Relative Skill of Those in the Art and The Amount of Direction or Guidance Presented***

The Patent Office appears to acknowledge that the relative skill of those in the art is high by asserting that the artisan practicing claims 154-159, 162-170, 173-190, 193-197, and 202 would be a physician with a M.D. and several years experience. More precisely however, is that where different arts are involved in the invention, the specification is enabling if it enables those skilled in each art, to carry out the aspect proper to their specialty. *See* MPEP § 2164.05(b) and cases cited therein. Thus, to illustrate, the relevant pool of people skilled in the art to practice the claims in question may include organic and/or medicinal chemists, for example, to synthesize the compound or to prepare formulations for administration to a subject, Ph.D.-level molecular biologists and biochemists to develop and perform screening assays such as are described in the specification, as well as pharmacologists or physicians as practitioners skilled in performing clinical studies. Applicants submit that, in any case, the relative skill of those in the art is high.

Keeping in mind the relative skill of those in art, Applicants submit that synthesizing the compounds to practice the claims in question is well within the abilities of one practicing the claims given the high skill in the art and the many different descriptions throughout the specification of how such similar compounds were synthesized. *See* specification, pp. 33-162. Selecting formulations (*e.g.*, page 21, line 29, to page 24, line 26), dosing regimens (*e.g.*, page 27, lines 4-22), and routes of administration (*e.g.*, page 26, line 31, to page 27, line 3) of the compounds are likewise within the abilities of one of skill in the art given the direction within the specification. The CXCR binding assay described on page 162, line 14, to page 163, line 14, teaches a method that can be used for evaluating the compounds and Figure 19 supplies representative data taken from exemplary compounds assayed using the method. This information, coupled with the knowledge already in the prior art regarding the dosing regimens of other chemokine inhibitors and with the instant disclosure, supplies one of skill with a solid basis for determining a therapeutically effective amount. Further, in contrast to the Patent Office assertion, there are numerous art-recognized *in vivo* disease models that could be used to test the compounds (*see, e.g.*, Gerard & Rollins, 2001, *Nature Immunology* 2:108-115, p. 109 tbl. I (**Exhibit 6**)), and as explained with regard to the state of the prior art, a mechanism involving CXCR3 dysfunction clearly underlies certain

inflammation-related and autoimmune disorders and diseases. What the prior art lacks, and what is supplied by the disclosure, is specific guidance on compounds to be used in the methods of claims 154-159, 162-170, 173-190, 193-197, and 202.

Applicants submit that both factors, the relative skill of those in the art and the amount of direction or guidance presented, weigh in favor that no undue experimentation is required for one of skill in the art to practice claims 154-159, 162-170, 173-190, 193-197, and 202.

3. *The Nature of the Invention and The Predictability or Unpredictability of the Art*

The Patent Office summarily concludes that the nature of the invention is the clinical treatment of disease which involves physiological activity (Office Action, p. 12), and states that physiological activity is generally recognized as unpredictable (Office Action, p. 14) with out further elaboration on the facts. Applicants disagree because here there is a firm connection between CXCR3 and certain pathological conditions, as discussed above with regard to the state of the prior art. To one extent Applicant agrees with the Patent Office: "[chemokines] have certainly been a difficult family to work with," but the Patent Office appears not to recognize that this passage from Proudfoot *et al.* is made to highlight the difficulties that have been seen finding small molecules that will act as chemokine inhibitors. *See* Office Action, p. 13 (quoting Proudfoot et al., p. 61, left col.). There is no unpredictability in designing an chemokine modulator for CXCR3, for example in with regard to the compound of claim 136 as recited in the method claims such as claim 187, since the specification is replete with guidance on the structure of such compound, as discussed above. Further, the specification provides evidence that the compound of claim 136 modulates CXCR3. Thus, the nature of claims 154-159, 162-170, 173-190, 193-197, and 202 are directed towards methods of treating certain recited CXCR-mediated conditions, and in light of the prior state of the art as discussed above, this *Wands* factor does not suggest finding undue experimentation.

With the link of CXCR3 to the conditions or diseases recited in claims 154-159, 162-170, 173-190, 193-197 and 202, Applicants submit that the burden is on the Patent Office to explain why the compound of 136 would not lend itself for one of skill to use the methods of claims 154-159, 162-170, 173-190, 193-197 and 202. Hence, Applicants respectfully submit that predictability or unpredictability in the art favors that no undue experimentation is required.

4. *The Presence or Absence of Working Examples*

The Patent Office alleges that there is no working example of treatment of any disease in man or animals. Applicants note that an *in vitro* or *in vivo* example in the specification is a working example supporting a claimed method if the example correlates with the claimed method. *See Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985); *In re Brana*, 34 U.S.P.Q.2d 1436, 1440 (Fed. Cir. 1995). The Patent Office bears the burden of giving reasons for lack of a correlation between the example and the claimed method. It is not a rigorous correlation but only a reasonable correlation between a disclosed *in vitro* utility and a claimed *in vivo* method that is necessary. *See Cross*, 224 U.S.P.Q. at 747. The instant specification provides a CXCR3 binding assay on pages 162-163 and provides data of exemplary compounds tested in Figure 19. Applicants submit that a reasonable correlation between the disclosed *in vitro* utility, *i.e.*, CXCR3 binding as exemplified by the compounds shown in Figure 19 of the specification, and methods of treating a CXCR3-mediated condition or disease including an inflammatory or immune condition or disease and cancer. Since the Patent Office has not offered a reason for lack of such a correlation, the presence or absence of working example *Wands* factor weighs against finding undue experimentation.

5. *The Quantity of Experimentation Necessary*

The Patent Office contends that a large degree of experimentation is required allegedly due to the necessities of synthesizing the compound, formulating it into suitable dosage form and subjecting the compound to clinical trials or an art-recognized disease model in order to determine if the compound would treat any particular human disease. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 U.S.P.Q. 428 (Fed. Cir. 1985). Applicants submit that the art typically engages in the experimentation identified by the Patent Office, as exemplified by numerous chemokine inhibitors currently in clinical testing. *See, e.g.*, Onuffer & Horuk, 2002, *Trends Pharmaco. Sci.* 23:459-467, p. 462 tbl. 2 (cited by Patent Office). What is more, the specification presents extensive guidance and examples on making and testing compounds. *See* specification, page 33, line 24, to page 163, line 22. Applicants submit that the quantity of experimentation necessary does not support a finding of undue experimentation.

6. *The Breadth of Claims*

The Patent Office asserts that the scope of the claims involves all of the thousands of compounds of claim 136 as well as the hundreds of diseases embraced by the term CXCR3-mediated condition or disease, and is therefore very broad. Applicants respectfully disagree.

The compounds of claim 136 have a common structure and the specification describes the synthesis of numerous compounds from which one of skill in the art can trace exemplary synthetic pathways for the production of a compound of claim 136. Figure 19 supplies evidence for predicting that compounds of claim 136 will be, to a large extent, CXCR3 modulators. In addition, the term "CXCR3-mediated condition or disease" is sufficiently described in the specification and known to those of skill in the art for the reasons discussed *infra*, Section VI.A.iii. Applicants submit that the breadth of claims factor sides with a finding of experimentation that is not undue.

Applicants respectfully submit that the *Wands* factors weigh against a finding of undue experimentation for claims 154-159, 162-170, 173-190, 193-197 and 202. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 154-159, 162-170, 173-190, 193-197 and 202 under 35 U.S.C. § 112, first paragraph.

B. Claim Rejections Under 35 U.S.C. § 103

i. Obviousness Rejection in view of U.S. Patent No. 6,545,005 ("Baxter '005")

Claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168, 169, 170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202-204 stand rejected under 35 U.S.C. § 103(a), allegedly for being obvious over U.S. Patent No. 6,545,005 ("Baxter '005"). Specifically, the Patent Office alleges that structurally dissimilarities between compound (20) of Baxter '005 and the compounds recited in the instant claims are taught internally in Baxter '005, and that the uses for the compound of Baxter '005 to treat cancer, psoriasis, etc., are identical to those recited in certain of the instant claims. Applicants respectfully traverse.

The Patent Office has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). To do so, the Patent Office must show some suggestion, teaching, or motivation within the prior art whereby a person of ordinary skill in the art would make the claimed combination. *Id.* at

1446. Generalization is to be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other. *In re Grabiak*, 226 U.S.P.Q. 870, 872 (Fed. Cir. 1985). The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 21 U.S.P.Q.2d 1941, 1943 (Fed. Cir. 1992). A reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. *In re Baird*, 29 U.S.P.Q.2d 1550, 1552 (Fed. Cir. 1994). Applicants respectfully submit that the Patent Office has not established *prima facie* obviousness since the Patent Office has not stated a teaching, motivation or suggestion from Baxter '005, or otherwise, to make a compound of claim 136 or of any claims dependent from claim 136.

Applicants submit that Baxter '005 does not fairly suggest a compound as recited in claims 136 or 173, or of any claims dependent from claims 136 or 173. For example, there is no suggestion or motivation to select the combination of options under variables of R_1, L, -X-Y-Z-, W and R_2 and other necessary selections in the generic formula of Baxter '005 compounds to produce a compound encompassed within the instant claims. Baxter '005 does not teach or suggest particular substitutions with regard to any specific chemical structures that are taught, and only lists numerous options for the many variables of the generic formulas.

As discussed below, the Patent Office focuses on compound (20) in its rationale for its rejection, but Applicants respectfully submit that this choice is guided through hindsight based upon Applicant's application since there is no teaching or suggestion in Baxter '005 to find this structure most relevant.[1]

The Patent Office acknowledges the important chemical differences in compound (20) from a compound of instant claim 136. These differences include a urea linkage in compound (20) in place of an amide linkage to the R^4 group in the compound of claim 136, and a methyl group attached to a nitrogen in compound (20) rather than an alkylene-heteroaryl group as an option for the -L-R^3 group in the compound of claim 136. Certainly, the interchange of an amide linkage for a urea linkage *and* a alkylene-heteroaryl group for a methyl group is a more extensive chemical alteration than the simple substitution of a sulfur atom for oxygen atom that the court in *In re Grabiak* found to be non-obvious in the absence of a teaching or suggestion. *See In re Grabiak*, 226 U.S.P.Q. 870, 872 (Fed. Cir. 1985).

[1] Applicants do not admit, and Applicant's remarks should not be construed as an admission, that Baxter '005 even has written description support for or enablement for compound (20).

Furthermore, the substitutions into compound (20) that the Patent Office would make are selected from disclosed alternatives for generic formulas that have an altogether different scope, and nothing in Baxter '005 appears to teach or suggest those substitutions into compound (20). Indeed, the changes that the Patent Office would put into compound (20) have no precedence in any one of the embodiments taught in Baxter '005. That is, not one of the fifty-plus embodiments shown in Baxter '005 have both an appropriate amide linkage in a combination where the nitrogen in the amide linkage is tri-substituted to include an alkylene-heteroaryl group missing from compound (20).

Applicants also respectfully submit that picking and choosing specific options for the variables from the generic formula of Baxter '005 in order to substitute these into compound (20) to arrive at a compound of claim 136 can only be had by resorting to Applicant's instant application to guide how the specific options for the variables are chosen. The Patent Office has not supplied any teaching, suggestion or motivation in Baxter '005 or elsewhere for selecting the particular substituents for introduction into compound (20).

Applicants submit a *prima facie* case of obviousness has not been made for the compound of claims 136-139, 142, 143, 145, 147, 149, for the compound as recited in the method claim 173, and thus a *prima facie* case of obviousness has not been made against claims 153-158, 162, 163, 165, 166, 168, 169, 170, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202-204 that depend from claims 136 or 173. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168, 169, 170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202-204 under 35 U.S.C. § 103(a).

ii. Obviousness Rejection in view of WO 01/19800

Claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168, 169, 170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202-204 stand rejected under 35 U.S.C. § 103(a), allegedly for being obvious over Baxter (WO 01/19800) essentially for the reasons cited with regard to Baxter '005 discussed above. The Patent Office alleges that the chemical modification to compound (20) of Baxter (WO 01/19800), which is identical to compound (20) of Baxter '005, is taught within claims 31-39 of Baxter (WO 01/19800). Applicants respectfully traverse.

As discussed above, to make a *prima facie* case of obviousness, the Patent Office must show some suggestion, teaching, or motivation within the prior art whereby a person of

ordinary skill in the art would make the claimed combination. Applicants respectfully submit that the Patent Office has not met this requirement.

The Patent Office contends that claims 31-39 of Baxter (WO 01/19800) are drawn to compound (20) when in fact this is clearly not possible since the only independent claim of claims 31-39, *i.e.*, claim 31, defines a generic formula wherein variable X is -NH-. Compound (20) does not fall within the generic formula of claim 31 since the equivalent to variable X in compound (20) is $-N(CH_3)-$. Thus, nothing in claims 31-39 of Baxter (WO 01/19800) can be understood to apply to substitutions to the chemical structure of compound (20). Applicants submit that Baxter (WO 01/19800) does not teach or suggest the compound recited in the instant claims. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 136-139, 142, 143, 145, 147, 149, 153-158, 162, 163, 165, 166, 168, 169, 170, 173, 174, 177, 179, 181, 183, 184, 187, 188, 190, 193-195, 197 and 202-204 under 35 U.S.C. § 103(a).

C. Double Patenting Rejection

Claims 136-139, 149, 153, 187-190, 193-197 and 202 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting allegedly as being unpatentable over claims 51, 66, 79, 97 and 110 of copending Application No. 10/164,690 (Attorney docket no. 11134-006-999). Applicants respectfully traverse since claims 51, 66, 79, 97 and 110 of copending Application No. 10/164,690 have been canceled by Supplemental Preliminary Amendment, mailed August 29, 2002. Accordingly, Applicants respectfully request that the obviousness-type double patenting rejection of claims 136-139, 149, 153, 187-190, 193-197 and 202 be withdrawn.

VII. ALLOWABLE SUBJECT MATTER

It is Applicants' understanding that the objection and the rejection to claims 140, 141, 144, 146, 148, and 150-152 were made solely in connection with the recitation of the term "prodrug" which is no longer recited in any of the pending claims. For this reason, Applicants earnestly solicit early notification that claims 140, 141, 144, 146, 148, and 150-152 are allowable.

Applicants respectfully submit that a typographical error is present on page 19, paragraph 21, of the Office Action mailed May 30, 2003, where the Patent Office refers to WO 01/16144 A (Ref. AT) rather than the appropriate reference WO 01/16114 A (Ref. AT). Applicants kindly request that the Patent Office verify that WO 01/16114 A (Ref. AT) is the

intended reference to be included in the Patent Office's statement of reasons for the indication of allowable subject matter in the Office Action mailed May 30, 2003.

CONCLUSION

In view of the above remarks, the subject application is believed to be in good and proper order for allowance. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 849-7607.

No fees other than those for the Petition for One Month Extension of Time are believed due with this response. However, the Commissioner is authorized to charge any fees under 37 C.F.R. § 1.17, any underpayment of fees, or credit any overpayment to Pennie & Edmonds$_{LLP}$ U.S. Deposit Account No. 16-1150 (order no. 11134-005-999) that may be required by this Amendment and Response.

Respectfully submitted,

Date: 6/15/03

42,983
Rahul Pathak (Reg. No.)
For: Anthony M. Insogna (Reg. No. 35,203)

PENNIE & EDMONDS LLP
12750 High Bluff Drive
Suite 300
San Diego, CA 92130
(858) 314-1200

EXHIBITS 1-6

1. Agostini *et al.,* 1998 *J. Immunology* 161:6413-6420

2. Sorensen et al., 1999, *J. Clinical Invest.* 103:807-815

3. Balashov *et al.*, 1999, *Proc. Natl. Acad. Sci. USA* 96:6873-6878

4. Qin *et al.*, 1998, *J. Clin. Invest.* 101:746-754

5. Shields *et al.*, 1999, *J. Immunology* 163:6236-6243

6. Gerard & Rollins, 2001, *Nature Immunology* 2:108-115